Women and Ischemia Syndrome Evaluation (WISE)
Diagnosis and Pathophysiology of Ischemic Heart Disease
Workshop

October 2-4, 2002

Session 4

1. Topic and Author

WHI Hormonal Influences: Future Opportunities
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2. Where we stand in 2002. Overview/rationale for inclusion of topic.

The WHI E+P study tested the most commonly used regimen of combined estrogen plus progestin consisting of conjugated equine estrogens 0.625 mg and medroxyprogesterone actetate 2.5 mg daily vs placebo. Treatment was terminated prematurely after an average of 5.2 years of follow-up as no benefit had emerged for coronary or cardiovascular events, and rates of invasive breast cancer were rising.

In contrast, the WHI Estrogen-only trial is continuing. This part of the program is testing conjugated equine estrogens 0.625 mg daily vs placebo in women who have had a hysterectomy. Women in the Estrogen-only trial had uniformly poorer cardiovascular and breast cancer risk profiles at baseline when compared to women in the E+P trial. It is monitored in an identical fashion to the E+P trial. Thus, at least at this point in time, a similar adverse risk/benefit ratio has not emerged with the estrogen alone regimen despite the poorer baseline risk loading in these women.

Most of the exposure reflected in the observational literature, especially the influential early studies, relates to estrogen alone therapy. If the WHI Estrogen-only study demonstrates a favorable benefit/risk profile the seeming paradox between the cardiovascular benefit seen in most observational studies and the harm found in HERS and the WHI E+P trial may be explained by the opposing effects of the progestin they tested which was identical in both trials. Medroxyprogesterone acetate has been shown to attenuate estrogen benefits on a variety of acute and long-term vascular outcomes. Progesterone, a weaker progestogen, has been shown in human and non-human primate studies to be substantially less attenuating while still providing endometrial protection.

Although hormone effects on lipids are clearly not the primary mechanism for the early excess of vascular events in the HRT trials, they are one common measure of progestogen potency. Norgestimate has estrogen, androgen and progesterone receptor-affinities similar to progesterone, and lipid effects midway between progesterone and medroxyprogesterone acetate. In contrast, norethindrone acetate has greater receptor affinity and attenuates estrogen effects on lipids more than medroxyprogesterone acetate. Thus, it is not clear that generalization of the WHI E+P results to regimens employing other progestins is appropriate. Study of these regimens is warranted. Within this class it seems likely that the weaker compounds that provide endometrial protection and have an acceptable bleeding profile would be of greatest interest.

Just as only one progestin has been evaluated in the major human studies with coronary endpoints, only one estrogen has been studied, conjugated equine estrogen. Head to head comparisons of this compound with 17-beta estradiol which some gynecologists believe may be more physiologic are lacking. However, unlike the progestogen data, studies of either of these two leading estrogens with similar designs have tended to yield similar results. Furthermore, estradiol can be administered both via oral and transdermal routes. First pass hepatic metabolism associated with oral use induces certain liver enzymes that may have both beneficial (eg LDL, HDL) and negative (eg, insulin resistance, hemostatic) effects.

The extent of disease at the time hormone treatment is started could influence the likelihood that estrogen will

be beneficial for an individual woman. It has been argued that the female advantage in coronary disease rates is attributable to primary prevention by estrogen before menopause, and that the acceleration in ischemic disease following menopause is due to the loss of this estrogen-related protection. Proponents of this hypothesis suggest that estrogen treatment does little to reduce event rates once atheromatous disease is established. If this is true, estrogen treatment would be beneficial if started every early in menopause, with subsequent dilution of benefit the longer after menopause it is begun. The mean age of WHI E+P women when they began treatment was 63 years, but analyses stratified by age did not suggest more protection in younger women. Issues of statistical power for subgroup analyses and possible attenuation by the medroxyprogesterone acetate make it difficult to view this result as conclusive. As a secondary prevention trial, HERS cannot address this either.

3. Current challenges and the most important issues for future research

Effects on breast cancer and coronary events in the WHI notwithstanding, estrogen plus progestogen therapy is rational for some women for benefits on vasomotor symptoms, urogenital health and quality of life effects. The attributable risk for the outcomes related to E+P tested in WHI was modest. There is ample data to question whether the WHI E+P results can be generalized to other combination HRT regimens, especially those with weaker progestogens. If the WHI E-only study finds a meaningful cardiovascular benefit this conclusion will be obvious. But since the E-only study is being conducted in women with greater cardiovascular and breast cancer risk than the women who in the E+P cohort, an equivocal result in that study will still leave questions of primary prevention in average risk women unanswered. Although long-term disease-event studies will ultimately be necessary, short-term studies using surrogate endpoints such as carotid intimal medial thickness might be an appropriate first step.

Human studies testing estrogen plus progesterone and other progestogens weaker than medroxyprogesterone acetate, and testing conjugated estrogens vs 17-beta estradiol, and oral vs transdermal administration, are warranted. HRT studies enrolling only young postmenopausal women could be useful if the WHI Estrogen-alone study suggests a greater benefit at younger ages.

Since progestogens are used only to protect the endometrium, if the WHI Estrogen-only study shows an improved benefit/risk ratio, it may be appropriate to evaluate locally acting progestogen delivery systems.

Not directly related to ischemic disease, but key to the benefit/risk balance, is the contribution of progestogens to breast cancer risk. Data are sparse on differential effects of progestogens in breast tissue. Studies in tissue culture suggest that medroxyprogesterone acetate is more potent in inducing tumor markers than progesterone. Mammographic studies of breast density may not be specific enough. Other strategies for answering this question should be explored.

4. Current challenges in the areas of communicating messages to health care community, patients and the public

The results of the WHI E+P study were widely reported. But the fact that those findings relate to a specific regimen that may not be generalizable was not appreciated by the lay community and some providers. Many clinicians are unaware of the data on contrasts between specific progestogens in target organs.

Some women remain very interested in using E+P combinations, many for quality of life concerns, and some for long-term benefits, but they and their health care providers are uncertain how to assess individual benefit/risk. Also, since the combination tested in the WHI has been so dominant in the US, clinicians have less experience and understanding of alternate progestins such as progesterone or norgestimate.

5. Translating new findings to improved diagnosis and treatment/saving lives.

The results of studies suggested here would greatly expand our understanding of hormone treatments. It would be unfortunate to over-generalize the WHI E+P results in a manner that could effectively deny women access to related treatments that may have a meaningfully different benefit/risk profile. The results of the investigations suggested here would assist women and clinicians who need to make informed choices in a complicated area

which nonetheless has significant impact on women's daily lives and long-term risk. Tools to place the benefits and risks of specific regimens in context for common categories of patients (eg, by age, personal and family risk status, etc) would also be useful.

6. References.

1) Adams MR, Kaplan JR, Manuck SB, Koritnik DR, Parks JS, Wolfe MS, Clarkson TB. Inhibition of coronary artery atherosclerosis by 17-beta estradiol in ovariectomized monkeys. Lack of an effect of added progesterone. Arteriosclerosis. 1990;10:1051-1057.
2) Adams MR, Register TC, Golden DL, Wagner JD, Williams JK. Medroxyprogesterone acetate antagonizes inhibitory effects of conjugated equine estrogens on coronary artery atherosclerosis. Arterioscler Thromb Vasc Biol. 1997;17:217-221.
3) Langer RD. Hormone replacement and the prevention of cardiovascular disease. Am J Cardiol. 2002 Jun 20;89(12 Suppl):36E-46E.
4) Miyagawa K, Rösch J, Stanczyk F, Hermsmeyer K. Medroxyprogesterone interferes with ovarian steroid protection against coronary vasospasm. Nat Med. 1997;3:324-327.
5) Rosano GM, Webb CM, Chierchia S, Morgani GL, Gabraele M, Sarrel PM, de Ziegler D, Collins P. Natural progesterone, but not medroxyprogesterone acetate, enhances the beneficial effect of estrogen on exercise-induced myocardial ischemia in postmenopausal women. J Am Coll Cardiol. 2000;36:2154-2159.
6) The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. JAMA, 1995; 273(3):199-208.
7) Williams JK, Adams MR, Klopfenstein HS. Estrogen modulates responses of atherosclerotic coronary arteries. Circulation. 1990;81:1680-1687.
8) Williams JK, Honoré EK, Washburn SA, Clarkson TB. Effects of hormone replacement therapy on reactivity of atherosclerotic coronary arteries in cynomolgus monkeys. J Am Coll Cardiol. 1994;24:1757-1761.
9) Writing Group for the Women's Health Initiative. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002 Jul 17;288(3):321-33.
10) Zhu X-D, Bonet B, Knopp RH. Estradiol 17-Beta inhibition of LDL oxidation and endothelial cell cytotoxicity is opposed by progestins to different degrees. Atherosclerosis. 2000;148:31-41.